Systems-Based Approaches to Food Protection and Security

Q&A

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Carol Ishimaru: The speakers will now join us for the panel discussion and questions from the audience.

Michelle Martin (University of Arkansas): Dr. Medford, have you found a chemical or pathogen that gives a false positive?

June Medford: Not yet, but we are testing for that rigorously. We are working with colleagues at Colorado State University to obtain microorganisms for application to plants for tests with drought and insects. The computational design in bacteria is specific. For instance, it picks up TNT—2,4,6-trinitrotoluene—it does not pick up 2,4- or 2,6-dinitrotoluene. As for pathogen specificity, Lindsay Triplett is just back from the Philippines and is looking at that. Basically, it's garbage in garbage out. Our components are signaling fairly well and we are testing them right now. I suspect that the computational design will be very specific, and what I can do with the pathogen ones with my toggle switch is add a threshold so that I can design around the low level of noise, just as a cell phone does that.

Sonny Ramaswamy (Oregon State University): Along those same lines, are you going to be looking for a generalist receptor or a specialist receptor, considering the multiplicity of ligands out there in the environment?

Medford: For things like explosives or nerve gas I want to be as specific as possible. If we are going to evacuate Mall of America then we want to know that the threat is real. For agricultural applications, I'm dependent on people in the community in terms of should I be more specific for an application or should I be general? I don't have all the answers.

Ramaswamy: If that's the case, you'd have a whole bunch of receptors on the plant that respond to, potentially, tens of thousands of chemicals and pathogens. How do you do that?

Medford: How many receptors can we put on there? We can now put in multiple computational designs as receptors. I'm not sure where we should go in terms of pathogen receptors—should we do one, two or more? A simple way would be to put out multiple sentinel plants.

Robert Buchanan (University of Maryland): A follow up—you have highly specific receptors and you could run into two situations. One: pathogens have a natural mutation rate and they have all kinds of exclusive mechanisms for beating receptor sites. So, what do you think the half-life of your receptor will be in effectiveness? Two: using these in fairly open locations, I could drive you crazy by setting them off, and after two or three times you would lose all faith in the receptor because of the consequences of false positives. How will you handle that?

Medford: Again, the computationally designed receptors are quite specific. We are looking for very specific ligands. Histidine kinase is involved in inter-bacterial quorum sensing and we are trying to target those that are specific to cells. These are signal molecules that bacteria typically use to say, "Okay we have a quorum." One of the challenges we have is to find the specificity. We can redesign receptors for small molecules. As for pathogens, we are working on that right now. The jury is still out. We do not want false positives, absolutely not.

Ramaswamy (Oregon State University): Dr. Winterfeldt, application of the game theory is fascinating, but much of what we have done in the United States has been reactive, almost like a chess game, trying to figure out what the terrorists are doing. Have you also considered actually getting to the core of the problem—not the bomb and bomber analogy, but actually going through the reasons why we have this situation today. Does your center look at that part of it, as well as what sort of risks and benefits one may get from actually addressing the core problem of where those terrorisms come from?

Detlof von Winterfeldt: We have looked at the problem, but we have not done a cost-benefit analysis on fixing it at the root cause. Another center, START[1], is a support organization that deals with causes of terrorism and motivations of terrorists. At CREATE, we have an exercise to understand the objectives of terrorists, which turns out to be interesting

[1]National Consortium for the Study of Terrorism and Responses to Terrorism.

because—in common parlance and in the media—it is always about killing Americans. Well, it's more than that. It's a lot more than that. It includes things like establishing fundamentalist regimes based in the Middle East and redeveloping respect. A complex web of values is involved, and it's hard from that angle to change things. One thing we know is that one big concern of fundamentalist terrorists has to do with the presence of the American military in the Middle East. A major objective is to get the Americans out of the Middle East. Now, I'm saying this rhetorically—I know how to fix that, right? But certainly it's not something I would throw on the policy table.

Frank Busta (National Center for Food Protection and Defense): Frequently in food safety we talk about minimal acceptable risk when trying to determine just how safe we need to be. Can you see how the work that you are doing will help politicians and public-health agencies come up with the ability to say that we will accept, let's say, one *E. coli* case per 100,000 people or a million people. And how do we sell that to the public?

von Winterfeldt: Well, this is a common problem. The Environmental Protection Agency has that problem and they are trying to prioritize risks based on what they know about consequences and threats. I don't think there is a magical number, when you say one in a million or that one outbreak in a year is okay. I think the real answer has to come from the cost effectiveness of the remaining risk-reduction options. At some point it gets too expensive; you are spending more money than you are reducing the risk, and you have to find that point. Ironically, it's different for different risks. For example, in highway safety you can save a life for about $50,000 dollars, roughly. In nuclear power to save a life you have to invest something like $10 million. At some point you cross a boundary of whether it's worth investing more money for risk reduction. But, I don't think there's an acceptable risk in absolute terms. What remains after you make all the prudent decisions is an acceptable risk.

Ishimaru: David, in terms of ecological assessment what are acceptable limits to risk?

David Andow: Dr. von Winterfeldt gave a more sophisticated answer than I will give. It's difficult to get anybody to talk about what they consider to be acceptable, and getting agreement on what is acceptable by approaching the subject directly is probably unrealistic. That's certainly true in terms of human lives, but also for the environment because not everybody is clear exactly how they think about these things, and so when you ask those kinds of questions you are asking for people to give you information on things they haven't thought through. So, you get gut feelings. The idea that the previous speaker suggested—to think about how much it costs to do certain things and to try to figure out ways of doing these things more cheaply, looking at the political consequences of those kinds of actions or proposals—gives you a better sense of what people are really willing to do. Also, in the environmental area, the issues are quite dynamic. They change in decadal timeframes; things that were acceptable 20 years ago are not necessarily considered acceptable currently.

Robert Buchanan (University of Maryland): Following up on Frank Busta's question and comment—the description you gave was basically the traditional approach where you would establish the stringency of your control systems, typically by establishing some kind of standard or frequency of inspection or some other activity where you were basically hiding your risk-management decisions from expert consideration. However, with the emergence of more sophisticated types of analysis, now it doesn't take people like me or others to just go back and say, "Okay this is what you did. This is the calculation that says this is what you are actually willing to tolerate." It's becoming a problem for policymakers and professional risk managers because they are not hiding out anymore. They have to deal with these things and I think we are on the cusp of a very important debate in terms of policy, particularly in the food area, because we can now calculate the number of potential cases, the number of deaths that occur, *etc*. I would love to hear your thoughts on that—where this debate and where the modern techniques of risk assessment are actually going to take the policymakers.

von Winterfeldt: There was a case, many years ago, concerning the Ford Pinto. The Ford Company had done a cost-benefit analysis of the risk of explosion due to a defective fuel system and found that they could avoid the risk for the trivial cost of about $50 per car. After several of these explosions, they were taken to court and this analysis came up, leading the judge to level huge punitive damages because the argument was like what you said: "We made this conscious decision not to make that $50 change because it wasn't cost effective." I recognize the problem, but I'm not sure what to do about it. Although in many ways it makes it more transparent if the decision is based on risk assessment, cost effectiveness, analysis and so on, I don't see what the alternative is. Keeping it nontransparent doesn't seem the right thing to do either. We have to deal with it and I think you will find much more willingness by at least the US-government agencies to be open and expressive about it—and that's encouraging—and then defend it. You don't have to go as far as putting a value on a life. You can do sophisticated analysis, break-even analysis, that says, "This saves so many lives and that's definitely worth spending $10 million." You don't have to go through the really crude calculations.

Ishimaru: June, in terms of your research, your technological approach to looking at surveillance and detection, what part of this conversation informs you in terms of molecules or agents that you are targeting. How do you reach conclusions? What kinds of assessment do you use to make decisions?

Medford: In terms of what we build detectors to—it's what the Department of Defense and people in the community say will work. So, Dr. Buchanan, you asked about specificity. I'm dependant on those who came before me who say, "I know this is the one that's specific." For the computational design, we have a limit in the size of the molecule. Ours is an emerging technology that provides tools for risk analysis and for people to make decisions. It does bring up an interesting thing: if we can detect a variety of compounds, where would we draw the line?

Ishimaru: But are there costs associated with the development of these technologies?

Medford: Our technology will be very inexpensive. I actually tried to fill out a Defense Department form, and I came down to pennies and it didn't fit onto the form. They were asking cost per unit.

von Winterfeldt: And you had these wonderful co-benefits.

Medford: But it does bring up the huge complexity of where do you guys draw the line of what is risk? If we can detect compounds everywhere inexpensively, where do you draw the line? How much contamination can we tolerate? That's not for me to do. I'm the scientist. You guys are the publicists.

Ishimaru: Along that line, though, some of the mandates that have come to DHS have affected scientists in terms of their ability to do research. In particular, the select-agent list has affected us quite a bit. Dr. von Winterfeldt, I noted from your comments about when you did a risk analysis of different agents—which are reported to have a higher risk associated with them—is that kind of information then going to inform decisions about things like select agents?

von Winterfeldt: I would think so. Certainly in my discussions at the time with the Department of Homeland Security officials—at a pretty high level—they were interested in having more work done on the high-threat, high-consequence spectrum. And so, in that sense, yes, I think it was leading to decisions in that area. And certainly in the nuclear area, we are investing a huge amount of money compared to biological or chemical. The nuclear defense system has a budget of $300 million a year just on that one issue. Again, risk analysis isn't easy with this business, so they actually established a fairly sizable group within the Department because so much of this is secret work that deals exclusively with risk analysis and risk management, and that group's intention is to inform the decision-makers inside the DHS to make better risk-informed decisions.

Francisco Diez-Gonzalez (University of Minnesota): A question for David. You talked about our need to incorporate cultural factors in risk-assessment, and I'm wondering whether—in the case of genetically modified wheat—have cultural factors over-ridden everything else? Varieties of GM wheat have been developed, but nobody is growing it as far as I know.

Andow: With GM wheat, there are economic issues as well as cultural issues. Perceptions of risks and benefits vary around the world. High-quality durum wheat is produced here, and sold where the best price is obtained. Those buyers may see few benefits and significant problems from, say, herbicide-tolerant wheat. So, their economic calculus will influence what they buy which will then have effects throughout the supply chain.

Ishimaru: In particular with wheat, an important global crop, that's a decision that is based on the particular nation's ability to feed itself, it's food security. Risks associated with GM wheat will probably outweigh other considerations simply because the crop is needed for basic food.

Andow: In some cases that will apply. Focusing on GM varieties in the Red River Valley, which produces high-quality durum wheats, may be inappropriate because of marketing issues.

Koel Ghosh (National Center for Food Protection and Defense): I want to visit the question of expert edification in risk assessment. Because answers given by experts often inform risk assessment, how do you go about managing—or what would be the best practices for—expert solicitation? And I have a secondary question for the whole panel. When you do risk assessment within an area—say ecological or terrorism—different attributes will define benefits and costs. When you combine these systems and are examining risk assessment as a whole—especially when you are considering sustainability within risk assessment—what would be the common denominator for leveling out the differences between the systems?

von Winterfeldt: There are standards for getting probability decisions from experts—protocols, tools—that have slight variations, but they pretty much are all similar in the sense that they consist of a conscious selection of the experts, not just willy-nilly people off the street, usually by set criteria of both expertise and diversity of opinion; it's important to have diversity in the pool of experts. That's one. The second one is that training is required because substantive experts typically are used to expressing their opinions in probabilities. So that takes some work. The third one is that it shouldn't just be "ask a question, get an answer." It should be a dialogue where the answer is documented with references to source information to support the argument. When I build a probability distribution, I typically have at least three points with well documented reasons. And then the third aspect is how you deal with multiple experts, and that is where you have some diversity of approaches. You can either do a consensus approach or you do a Delphi or whatever to bring them together, but, in the end, you have to combine them. What we have learned in those processes is that the disagreement among the experts is often huge and the arguments often come from basic assumptions that they make. It's not about small variations in probabilities. It's important to document that as well. On common metrics—yes there are always many attributes that you have to consider. Cost is one, health is another one, cultural impact values is another, and ecosystem impact is another. I, actually, prefer not to roll them into one, but to keep them apart and do the analysis. So, for example, in our very simple example of milk we had morbidity, mortality, indirect and direct economics, and, of course, cost of intervention. We kept them apart; we didn't roll them up. It's useful to keep them apart for as long as you can.

Andow: In the environmental area, we like to think that we can get to a single metric at some point, but actually we don't achieve that often. A lot of the risk-assessment meth-

odologies are aimed at coming to a determination of no significant risk. So, there are lots of findings of no significant impact, rather than trying to get some value associated with it. And then when there are risks, such as with pesticide use; the idea is to modify the management system to reduce those risks. A lot of approaches on the environmental side aren't oriented to trying to get into a metric. When we do go that way we tend to not have enough data to really fill that out, so the expert solicitation process tends to produce more crude ranking methods, in which case the confidence you might have in that in terms of "this means this much value" is undermined somewhat. So, then we tend to maintain these multiple criteria and start asking if we understand the tradeoffs between them as we go into decision-making. On the other side, we sometimes take specific criteria that aren't related to monetary value specifically, and key in a decision off of that. For example, in resistance evolution one of the key variables is how long it will be before resistance failures occur, so then you orient a lot of the information around that and, of course, the longer you push that the more expensive it may be. There's a number of variables and covariables and that is the framework that the decision-maker ends up using.

Ishimaru: Martin, in terms of detection and prevention, you focused a lot on technology and improving sensitivity and specificity, but in terms of the chain of events that produce a hamburger and milk, are you looking at specific components within that in terms of risk of where there might be certain places that you would want to target that detection?

Duplessis: In the food industry right now, programs are in place that already identified potential risks along food-supply chains (*e.g.* HACCP[2], the CARVER+Shock Vulnerability Assessment tool). In our project, we designed our detection system to make sure that it can be used anywhere during food-processing/production steps, from farm to fork. Our system is flexible and can be customized to detect pathogens in food samples, but also in environmental samples for monitoring and surveillance purposes. We have not targeted specific risks where we wanted to target detection.

Ishimaru: Also, we understand more about the ecology of the microorganisms in our food and that they often come from plants or soil. But we haven't done a good job of connecting that chain of events from plants growing in the field to their purchase in the supermarket, and identifying points of vulnerability. One more question.

Jozef Kokini (University of Illinois): This is for the whole panel. How close are we in terms of developing truly impactful and practical tools? For example, in terms of the competition that we have for risk assessment, are we at the point where the Department of Defense is able to use these tools and, therefore, come up with better defense strategies? One speaker talked about tools focused on nanotechnology. Of these, which are closer to delivering tools that can actually be used to reduce risk? Another speaker talked about taking us through a small garden of plants. How close are we to having this at the airport instead of going through x-ray machines?

[2]Hazard analysis and critical control points, see footnote, page 211.

Duplessis: In terms of microfluidics, nanoparticles and so on, we are still quite far from field use. There are examples, such as biosensors, that may be useful in the short term, but the major challenge will be the cost of those new technologies. And we need to validate those assays, sometimes requiring people with technical expertise to use them. Technologies are moving faster and faster, and we are making progress, but funding for multidisciplinary teams is needed to solve complex issues. It will be a while before a microfluidic device will be available for use in the food industry.

Ishimaru: June, do you want to follow up on the question of using plants instead of x-ray machines?

Medford: Yes, walking through a greenhouse rather than through the typical TSA thing—as soon as possible. People in the Department of Defense have told me that if we had our plants working in the field today, they would use them today. So, we are addressing a real, critical need. I had hoped to have a field test done this summer. We are a bit behind. I'm thinking if the DOD gives me the money, I would love to do it this winter in Hawaii, but they may not go for that. They want me to go to Mississippi and test it. Mississippi versus Hawaii? Okay. We hope to get some prototypes out in a year or two. So, hopefully in the near future—our work is growing.